PATENT COOPERATION TREATY

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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
RE/B45171		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/01457	22/02/2000	25/02/1999
International Patent Classification (IPC) or national classification and IPC A61K39/385		
Applicant SMITHKLINE BEECHAM BIOLOGICALS S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01/08/2000	29.05.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Renggli, J Telephone No. +49 89 2399 7461

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/01457

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-36 as originally filed

Claims, No.:

1-20 as received on 25/01/2001 with letter of 24/01/2001

Drawings, sheets:

1/7-7/7 as originally filed

Sequence listing part of the description, pages:

1-3, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 20 with respect to industrial applicability.

because:

   ☒ the said international application, or the said claims Nos. 20 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*): **see separate sheet**

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-20
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-20
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

ITEM III:

Claim 20 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

ITEM V:

1. Reference is made to the following documents:

D1 US 5,858,677
D2 WO 97/31948

2. Industrial applicability (Art. 33(4) PCT):

The subject-matter of claims 1-19 is susceptible of industrial application.

For the assessment of the present claim 20 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

3. Novelty (Art. 33(2) PCT):

D1 describes the solubilization, purification and cloning of protein D from H. influenzae. This protein, conserved in many strains of Haemophilus influenzae, is thus suitable as an immunogenic component for producing a vaccine against H. influenzae (see column 2, lines 63-column 3, lines 10). The said vaccine may contain protein D or portions thereof and be combined with an immunogenic portion of another molecule (c3, l. 36-49).

There is no specific disclosure in D1 of a peptide coupled to protein D from Haemophilus influenzae, wherein said peptide is between 2-50 amino acid residues in length.

The subject-matter of claim 1 is thus novel over document D1. It follows that claims 2-20 meet also the requirements for novelty over D1.

D2, which discloses immunogen constructs comprising a carrier and IgE mimotopes (see D2, page 27 and page 10, first paragraph), does not disclose specifically the use of protein D as carrier and thus claim 1 is also novel over D2. It follows that claims 2-20 meet the requirements for novelty over D2.

4. Inventive step (Art. 33(3) PCT):

D2 is considered to be the closest prior art document, as it discloses the use of a carrier molecule in combination with IgE mimotopes (see D2, page 27 and page 10, first paragraph).

It has been shown in the present application that the use of protein D as carrier in combination with IgE mimotopes gives rise to a much better immune responses towards the said mimotopes.

This is apparently due to the low antibody response generated by the protein D carrier when compared with the carrier KLH, which was also used as carrier in document D2 (see description of the present application, Table 4, page 20; Table 7, page 22; example 8, pages 27-28).

The problem to be solved over D2 by claim 1 of the present application can thus be seen as the provision of an immunogenic carrier construct which provides a stronger immune response against the carried peptide.

The solution to this problem consists in the use of protein D as carrier molecule.

This solution cannot be derived in an obvious way from D1, or from any other document, since D1 concerns the use of protein D as an immunogenic vaccine

component against H. influenzae and thus does not concern or suggest the use of said protein as a weakly immunogenic carrier.

Claim 1 is thus inventive over the cited prior art. It follows that claims 2-20 meet the requirements for inventiveness over the cited prior art.

ITEM VI:

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 99/16884	8.4.1999	17.9.1998	26.9.1997

The above document, which has an earlier priority date than the present application may become relevant in the regional phase of the application.

ITEM VII:

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document WO 99/16884 is not mentioned in the description, nor is this document identified therein.

2. The application number on pages 6 and 13 should have been replaced by the corresponding publication number (cf. PCT Guidelines, PCT Gazette-Section IV, II-4.17).

Claims

1. An immunogen comprising a peptide and Protein D from Haemophilus Influenzae, or a fragment thereof as a carrier.
2. An immunogen as claimed in claim 1, wherein the peptide is between 2-50 amino acid residues in length.
3. An immunogen as claimed in claim 1 or 2, wherein said peptide is derived from one of an IgE epitope or mimotope, Gonadotrophin hormone releasing hormone or mimotope thereof, a fragment of the amyloid precursor protein or mimotope thereof.
4. An immunogen as claimed in any of claims 1to 3 wherein the ratio of peptide: protein D carrier is 1:20.
5. An immunogen as claimed in claim 4 wherein the ratio of peptide:protein D carrier is 2:10 peptides per protein D carrier.
6. An immunogen as claimed in any of claims 1 to 5, wherein the peptide is Aβ43 from the amyloid precursor protein or a fragment thereof.
7. An immunogen as claimed in claim 6 wherein the fragments are peptides selected from the group of peptides incorporating residues Aβ1-5, 1-12, 13-28, 17-28 and 33-42.
8. An immunogen as claimed in any one of claims 1 to 5 comprising the sequence EHWSYGLRPG as a tandem repeat conjugated to protein D through a central cysteine.
9. An immunogen as claimed in any of claims 1 to 5 derived from an IgE epitope selected from the group of peptides having the following sequences:

   KTKGSGFFVF

   EDGQVMDVD

   STTQEGEL

   SQKHWLSDRT

   GHTFEDSTKKCADSNPRGV
10. An immunogen as claimed in any of claims 1 to 5 wherein the mimotopes are selected from the group having the following sequences:

    CADSNPRGV

CLEDGQVMDVDLL-NH2

CSTTQEGELA- NH2

CSQKHWLSDRT- NH2

11. An immunogen as claimed herein wherein the protein D carrier is conjugated to a plurality of discrete peptides.

12. A vaccine comprising an immunogen as claimed herein and a pharmaceutically acceptable excipient.

13. A vaccine as claimed in claim 12 additionally comprising an adjuvant.

14. A vaccine as claimed in claim 13 wherein the adjuvant is selected from Saponin adjuvants, lipid A or derivative thereof, aluminium salt, oil in water emulsions, liposomes or combinations thereof.

15. A vaccine as claimed in any of claims 12 to 14 for use in medicine.

16. An immunogen as claimed in any of claims 1 to 11 for use in medicine.

17. Use of an immunogen as claimed herein, in the manufacture of a medicament, for the treatment or prophylaxis of an infectious or chronic disease.

18. A method of manufacturing an immunogen as claimed in any of claims 1 to 11 comprising the step of conjugating a peptide to protein D or a fragment thereof.

19. A method of manufacturing a vaccine as claimed in any of claims 12 to 15 comprising formulating an immunogen any of claims 1 to 11 with a pharmaceutically acceptable excipient.

20. A method of treating a patient suffering from or susceptible to a chronic or infectious disease comprising administering a safe and effective amount of vaccine or immunogen as claimed herein.